Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Melsew et al., J AIDS Clin Res 2013, 4:5
DOI: 10.4172/2155-6113.1000211

Research Article Open Access

Rate of Immunological Failure and its Predictors among Patients on Highly Active Antiretroviral Therapy at Debremarkos Hospital, Northwest Ethiopia: A Retrospective Follow up Study

Yayehirad Alemu Melsew[1], Mamo Wubshet Terefe [2], Gizachew Assefa Tessema[3] and Tadesse Awoke Ayele[4]*

[1]Department of Biomedical Sciences, College of Medicine and Health Science, Mizan-Tepi University, MizanTeferi, Ethiopia
[2]Department of Environmental and Occupational Health Safety, Institute of Public Health, University of Gondar, Ethiopia
[3]Department of Reproductive Health, Institute of Public Health, University of Gondar, Ethiopia
[4]Department of Epidemiology and Biostatistics, Institute of Public Health, University of Gondar, Ethiopia

Abstract

Background: In a resource-limited setting, patients on antiretroviral treatment are monitored by using immunological and clinical assessment due to the inaccessibility of viral load monitoring. The aim of this study was to assess the rate and predictors of immunological failure among patients taking highly active antiretroviral treatment at Debremarkos hospital, Northwest Ethiopia.

Methods: Retrospective follow up study was conducted at Debremarkos hospital on 509 adults who had started antiretroviral treatment during the period between January 01, 2007 and April 01, 2008. Data were analyzed using SPSS version 20. Life table and Kaplan-Meier curve were used to estimate the cumulative probablities and median time for immunologic failure respectively. Cox proportional hazard model was fitted to compute hazard ratios with their 95% confidence intervals.

Results: The median follow up time was 36 months (Inter Quartile Range (IQR) = 12-49 months). 107 (21%) patients had developed immunological failure with a failure rate of 8 per 100 patient-years of follow up. Recurrent pneumonia infection (Adjusted Hazards Ratio (AHR)=1.62, 95% CI: 1.10, 2.40), unemployment (AHR: 1.74, 95% CI: 1.11, 2.74), inability to work due to health problem (AHR= 2.19, 95%CI: 1.20, 4.02), baseline CD4 count ≤ 100 cells/mm^3 (AHR: 2.16, 95% CI: 1.44, 3.25) and change in body weight (AHR: 4.34, 95% CI: 2.93, 3.23) were significant predictors of immunological failure.

Conclusion: The immunological failure rate was found to be high. Recurrent pneumonia infection, being unemployed, inability to work, baseline CD4count less than 100 cells/mm^3 and decrease in body weight were predictors of immunological failure. Early initiation of highly active antiretroviral treatment, attempt to improve Socio-economic status of patients, and counseling patients to have protein rich diets would prevent early immunologic failure.

Keywords: Immunological failure; HAART; Cox-Regression; Ethiopia

Introduction

According to World Health Organization (WHO), globally there were about 34 million people living with HIV in 2011 [1]. Sub-Saharan Africa continues to bear an inordinate share of the global HIV burden. There were about 23 million people living with HIV/AIDS in this region [2]. Ethiopia belongs to the heavily affected countries, at having an estimated 1.2 million people living with HIV/AIDS in 2010 with a prevalence of 1.5 percent [3,4].

Highly active antiretroviral treatment (HAART) has been effective in prolonging and improving the quality of life of people living with HIV by transforming it from a fatal acute disease to a manageable chronic condition [5]. According to Ethiopian Federal HIV/AIDS Prevention and Control Office, there were 246, 347 people who ever started antiretroviral treatment (ART) [6].

The requirment of consistent and lifelong use of medication to reduce the possibility that the virus will adapt and become resistant to the drug is one of the challenge [5,7]. Antiretroviral treatment (ART) failure is associated with virologic failure, immunologic failure, and/or clinical failure. Virological failure is said to be occurred when plasma viral load become above 5000 copies/ml. Whereas immunological failure is defined as a fall in CD4 count to baseline (or below) or a 50% reduction from on treatment peak value or presence of persistent CD4 count below 100 cells/mm^3. In addition, clinical failure is the occurrence of new or recurrent WHO stage 4 conditions [8].

In Ethiopia, the criterion for the initiation of HAART is/are WHO stage IV irrespective of CD4 cell count or CD4 cell count less than 200 cell/mm^3 or total lymphocyte count below 1200/mm^3 if available [9]. Treatment failure may leads to the development of drug resistant virus strains which can be another treat to the world if this virus starts to transmit in the population [10,11]. Early detection of treatment failure is crucial to sustain first-line therapy effectiveness [5,7]. Viral load monitoring is the gold standard method to diagnose ART failure [12]. However, it is generally not accessible in resource-limited settings [13,14]. Hence, WHO recommends clinical and immunological

***Corresponding author:** Tadesse Awoke Ayele, Department of Epidemiology and Biostatistics, Institute of Public Health, University of Gondar, Ethiopia, E-mail: tawoke7@gmail.com

Received April 15, 2013; **Accepted** May 28, 2013; **Published** June 05, 2013

Citation: Melsew YA, Terefe MW, Tessema GA, Ayele TA (2013) Rate of Immunological Failure and its Predictors among Patients on Highly Active Antiretroviral Therapy at Debremarkos Hospital, Northwest Ethiopia: A Retrospective Follow up Study. J AIDS Clin Res 4: 211. doi:10.4172/2155-6113.1000211

assessment as a surrogate measure of viral load for monitoring patients on HAART [15] even though the sequential nature of treatment failure is not strongly evidence based and might take years to happen [16].

In Ethiopia, patients on HAART are monitored with immunological and clinical assessment. Hence, assessing the rate and predictors of immunologic failure will provide information for clinicians for appropriate management of patients on HAART. Moreover, policy makers and public health professionals can use the findings to design ART related programs.

Methods

A retrospective follow up study was conducted at Debremarkos Hospital, Northwest Ethiopia in April 2012. Debremarkos hospital is a referal hospital located at Debremarkos town, Northwest Ethiopia. The hospital, with 137 beds, serves for about 3.5 million people. There were a total of 8042 clients registered in HIV chronic care clinic out of them 4490 had ever started ART. The study populations were those patients who are 15 years old and above and ever started ART at Debremarkos Hospital. Those who had at least 6 months of follow up (having at least two CD4 measurements) and started ART during the period between January 01, 2007 and April 01, 2008. This period was selected to follow the patients for sufficient time. 509 clients fulfilled the inclusion criteria and hence included in this study. Three trained data collectors who have BSc in nursing from the date of HAART initiation to April 30, 2012 by using data extraction format reviewed the medical records of these patients.

The *event* of this study was immunological failure, defined as a fall in CD4 count to baseline (or below) or a 50% reduction from on-treatment peak value or presence of persistent CD4 count below 100 cells/mm^3 [3]. Patients, who were lost, died, transferred out or didn't show the event until the last visit was considered as *censored* .

Data were entered and cleaned by using Epi-Info version.3.5.3 then exported to SPSS version 20 statistical software for further analysis. Descriptive and summary statistics were conducted. Life table was used to estimate the cumulative probabilities. Kaplan–Meier survival curve was also used to estimate the median survival time from initiation of antiretroviral therapy to immunologic failure. Log rank test was used to compare the survival times at different categories of each independent variables. Bivariate and multivariate Cox-proportional hazard model were fitted to identify predictors of immunological failure. Hazard Ratio (HR) with 95% confidence intervals was computed and statistical significance was considered with P-value less than 0.05.

Ethical clearance was obtained from the ethical review board of the Institute of Public Health, University of Gondar. Formal letter of permission was also obtained from Debremarkos hospital administration.

Results

Baseline socio-demographic characteristics of patients

A total of 509 patients' records were reviewed for baseline and follow up measurements. Nearly three out of five (59.3%) patients were females. The median age of patients at the start of ART was 35 years (Inter Quartile Range (IQR) = 29 - 40). One hundred eighty six (36.5%) of the study participants had no formal education and 481(94.5%) of them had disclosed their HIV status (Table 1).

Baseline clinical characteristics of patients

Majority (86.2%) of patients had more than one opportunistic infection at the time of their HAART initiation. Slightly more than half (54.0%) of patients were working by their functional status and 398 (78.2%) patients had hemoglobin measurement of greater or equal to 10 mg/dl at the start of HAART. One hundred ninety five (38.3%) and 163 (32.0%) patients had started treatment with Stavudine-Lamivudine- Nevirapine and Zidovudine-Lamivudine-Nevirapine regimen respectively.

Three hundred eighteen (62.5%) patients were eligible by the criteria of CD4 count less than 200 cells/mm^3 whereas 162 (31.8%) patients were eligible by both CD4 below 200 and WHO stage II or III with total lymphocyte count (TLC) less or equal to 1200. The median baseline CD4 cell count was 117cells/mm^3 (IQR=63 - 162) (Table 2).

Immunological failure after initiation of highly active anteretroviral treatment

Study participants were followed for a minimum of 6 and maximum of 63 months with a median follow up time of 36 months (IQR:12-50months). 107 (21%) patients were found to have immunological failure. The cumulative probability of survival at 6, 12, 24, 36 and 60 months were 88%, 82%, 79%, 77% and 69% respectively (Figure 1).

Participants were followed for different period and the total person-time of follow up was 1334.42 patient-years of follow up. Hence, the rate of immunological failure was 8 per 100 patient-years of follow up.

Recurrent pneumonia infection, unemployment, inability to work due to ill health, baseline CD4 count ≤100 cells/mm^3 and weight change were found to be significant predictors of immunological failure in the multple Cox-regression analysis (Table 3).

Variables	Frequency	Percent
Sex		
Female	302	59.3
Male	207	40.7
Age (years)		
15-24	54	10.6
25-34	209	41.1
35-44	185	36.3
45-54	49	9.6
55+	12	2.4
Religion		
Orthodox	486	95.5
Muslim	18	3.5
Protestant	5	1.0
Employment		
Employed full time	212	41.7
Unemployed	194	38.1
Not working due to ill health	57	11.2
Employed part-time	46	9.0
Level of education		
no formal education	186	36.5
Primary	144	28.3
Secondary	136	26.7
Tertiary	43	8.4
Residence		
Urban	294	57.8
Rural	215	42.2

Table 1: Baseline Socio-demographic characteristics of HIV/AIDS patients on antiretroviral therapy at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Characteristics	Frequency	Percent
Eligibility criteria		
Only CD4 below 200	318	62.5
CD4 below 200 and WHO stage IIor III with TLC ≤ 1200	162	31.8
Both CD4 below 200 and WHO stage IV	22	4.3
WHO stage II and III with TLC ≤ 1200	7	1.4
Functional status		
Working	275	54.4
Ambulatory	222	44.0
Bedridden	8	1.6
WHO clinical stage		
Stage I	1	0.2
Stage II	40	7.9
Stage III	451	88.8
Stage IV	16	3.1
Baseline CD4 count		
≤ 100 cell/mm^3	212	41.7
>100 cell/mm^3	297	58.3
Drug type at initiation		
d4t - 3TC- NVP	197	38.7
d4t - 3TC- EFV	97	19.1
AZT – 3TC- NVP	163	32.0
AZT – 3TC- EFV	52	10.2
Hemoglobin level		
<10 mg/dl	70	15.0
≥ 10 mg/dl	398	85.0

Table 2: Baseline Clinical characteristics of HIV/AIDS patients on antiretroviral therapy at Debremarkos Hospital, Northwest Ethiopia, May 2012.

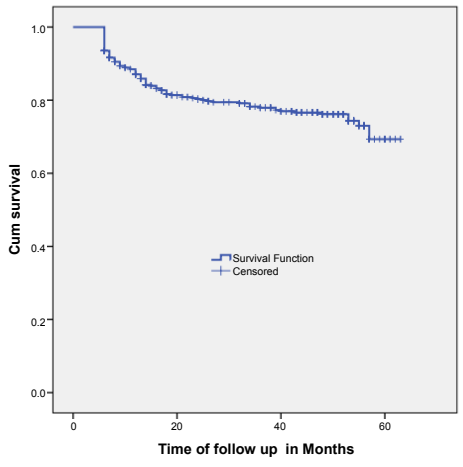

Figure 1: Kaplan Meir curve for immunological failure of HIV infected patients taking antiretroviral therapy at Debremarkos hospital, Northwest Ethiopia, May 2012.

Patients having recurrent pneumonia infection at the baseline were 1.62 times more likely to have immunological failure compared to those patients without recurrent pneumonia infection (AHR=1.62, 95%CI: 1.10, 2.40).

Unemployed patients were 1.74 times more likely to have immunological failure compared to those employed patients (AHR=1.74, 95%CI: 1.11, 2.74). Similarly patients who were not working due to health problem had about 2.19 times greater risk of immunological failure compared to working patients at the initiation of ART (AHR=2.19, 95%CI: 1.20, 4.02).

With respect to baseline CD4 cell count, those patients with baseline CD4 count ≤ 100 cells/mm^3 were 2.16 times more likely to have immunological failure compared to those patients with CD4 count greater than 100cells/mm^3 (AHR=2.16, 95%CI: 1.44, 3.25).

Weight change was also significant predictor of immunological failure. Those patients who had constant or a reduced body weight were 4.34 times more likely to have immunological failure compared to those patients with improved body weight (AHR=4.34 95%CI: 2.93, 6.41).

Discussion

In a resource limited settings assessment of HAART failure using viral load criteria is not possible due to the expensiveness of the instrument, rather clinical or immunologic criteria have been used to examine treatment failure. This study aimed to determine the rate and predictors of immunological failure among patients taking highly active antiretroviral treatment at Debremarkos hospital, Northwest Ethiopia. This study showed that the immunological failure rate was 21% (95% CI: 17.5%, 24.5%).

Among all 107 immunological failures 33(30.8%) patients were failed at 6 month while 62 (57.9%) were failed at 12 months of follow up. This finding revealed that more than half of the immunological failure occurred in the first 12 months of HAART initiation. The rate of immunological failure after 63 months on ART was 8 per 100 patient-years of observation. This finding is higher than a study conducted in Africa (2.64 per 100 patient-years) [17]. This might be due to the difference in socio-economic settings between the areas where the systematic review was conducted and the current study.

Variable	Immunological Status		HR(95% CI)	
	Failed	Censored	Crude HR [95% CI]	Adjusted HR [95% CI]
Sex				
Male	53	154	1.19[0.98, 1.44]	
Female	54	248	1	
Recurrent Pneumonia(> two times)				
Yes	63	263	1.39 [0.94, 2.04]	1.62[1.10, 2.40]*
No	44	139	1	1
Recurrent URTIs				
Yes	36	182	1.53 [1.02, 2.28]*	
No	71	220	1	
Employment				
Employed full time	32	180	1	1
Employed part time	10	36	1.58[0.78, 3.21]	1.58[0.77, 3.23]
Not working due to health problem	17	40	2.12[1.18, 3.88]*	2.19[1.20, 4.02]*
Unemployed	48	146	1.62[1.03, 2.53]*	1.74[1.11, 2.74]*
Weight Change				
Positive	48	323	1	1
No/negative	59	79	3.53[2.406, 5.164]*	4.34 [2.93, 3.23]*
Baseline CD4				
≤ 100cells/m^3	63	149	2.18[1.48, 3.20]*	2.16 [1.44, 3.25]*
>100cells/m^3	44	253	1	

*found significant at 0.05 level of significance

Table 3: The Cox-Regression output for predictors of immunological failure among patients taking ART at Debremarkos Hospital, Northwest Ethiopia, May 2012.

Patients having recurrent pneumonia infection at the initiation of HAART were 1.62 times at higher risk of immunological failure compared to those patients without recurrent pneumonia. The reason could be those patients who suffer from recurrent pneumonia might go through a more immunosuppressed state. Unemployed patients had about 1.74 times at higher risk of immunological failure compared to those employed patients. Moreover, patients who were not able to work due to health problem had 2.19 times at greater risk of immunological failure compared to worker patients at the start of HAART. This might be due to the reason that those worker patients may have better income that in turn creats opportunity to get better care and support. Those patients unable to work due to health problem were also at higher risk of immunological failure compared to working patients. This could be explained as patients who were unable to work might be in their advanced stage of the disease aggraviated from greater immunosuppression.

Patients with baseline CD4 count of less or equal to 100 cells/mm^3 were 2.16 times more likely to have immunological failure compared to those patients with CD4 count greater than 100 cells/mm^3. This finding is in line with a study conducted in Thailand [18] and South Africa [7]. This might be due to the reason that patients with baseline CD4 count of less or equal to100 cells/mm^3 are at a lesser immunity.

Patients who had constant or reduced body weight from the baseline had 4.34 times at risk of immunological failure compared to those patients with an improved body weight. This finding is consistent with a study done in India [19]. This could be explained as; an increase in body weight might be due to better diet and then better health this in turn may be due to improvement of immunity including increase in CD4 cells.

The limitation of this study was that since failure was only measured by immunological criteria it may not assure the presence of treatment failure. Being retrospective may limits the study to find out more predictors than those recorded in the charts.

Conclusions

In this study, there was high early immunological failure. More than half of immunologic failures occurred during the first 12 months of ART initiation. Having recurrent pneumonia infection at baseline, being unemployed, inability to work due to health problem, baseline CD4 count and body weight change were predictors of immunological failure. Early initiation of highly active antiretroviral treatment, attempt to Improve Socio-economic status of patients and monitoring using viral loads will be associated with improved outcomes.

Acknowledgment

We are very grateful to the University of Gondar for technical and financial support of this study. We would also like to thank Debremarkos hospital administration and staffs for giving permission and facilitate the data collection.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

YAM wrote the proposal, participated in data collection, analyzed the data and drafted the manuscript. MWT, GAT and TAA approved the proposal with some revisions, participated in data analysis and revised subsequent drafts of the paper. All authors participated in the preparation of the manuscript and approved the final manuscript

References

1. WHO (2010) WHO Regional HIV and AIDS statistics.
2. USAID (2011) HIV/AIDS Health Profile. Sub-Saharan Africa.
3. Federal Ministry of health HIV/AIDS Prevention & Control Office (2009) Strategic Plan for in Tensifying Multisectoral HIV and Aids Response in Ethiopia II (SPM II) 2009 – 2014. Addis Ababa, Ethopia
4. CSA, ICF Macro (2011) Ethiopian Demographicand Health Survey 2011. Central Statistical Agency and ICF international 2011: Preliminary Report. Addis Ababa, Ethiopia and Calverton, Maryland, USA.
5. World Health Organization (WHO) (2008) Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. Progress report 2008, 1-77.
6. Ministry of Health (2010) Federal HAPCO Update as of end of Tir 2002 Monthly HIV Care and ART Update.
7. El-Khatib Z, Katzenstein D, Marrone G, Laher F, Mohapi L, et al. (2011) Adherence to Drug-Refill Is a Useful Early Warning Indicator of Virologic and Immunologic Failure among HIV Patients on First-Line ART in South Africa. PLoS One 6: e17518
8. Stanecki K, Daher J, Stover J, Beusenberg M, Souteyrand Y, et al. (2010) Antiretroviral therapy needs: the effect of changing global guidelines. Sex Transm Infect 86 Suppl 2: ii62-66.
9. Federal HIV/AIDS Prevention and Control Office Federal Ministry of Health (2007) Guidelines for implementation of the Antiretroviral therapy programme In Ethiopia. Addis Ababa, Ethiopia.
10. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell ML (2011) Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South African adults. PLoS One 6: e21795.
11. Petersen ML, van der Laan MJ, Napravnik S, Eron JJ, Moore RD, et al. (2008) Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS 22: 2097-2106.
12. Keiser O, MacPhail P, Boulle A, Wood R, Schechter M, et al. (2009) Accuracy of WHO CD4 cell count criteria for virological failure of antiretroviral therapy. Trop Med Int Health 14: 1220-1225.
13. Harries AD, Zachariah R, van Oosterhout JJ, Reid SD, Hosseinipour MC, et al. (2010) Diagnosis and management of antiretroviral-therapy failure in resource-limited settings in sub-Saharan Africa: challenges and perspectives. Lancet Infect Dis 10: 60-65.
14. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, et al. (2007) HIV viral load monitoring in resource-limited regions: optional or necessary? Clin Infect Dis 44: 128-134.
15. WHO HIV/AIDS Programme (2006) Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for public health approach, 2006 revision.
16. Boyd MA (2010) Current and future management of treatment failure in low- and middle-income countries. Curr Opin HIV AIDS 5: 83-89.
17. Renaud-Théry F, Duncombe C, Kerr S, Thierry S, Perriëns J (2008) Adult antiretroviral therapy in resource limited settings: a systematic review of first-line failure and attrition rates. Geneva: WHO.
18. Khienprasit N, Chaiwarith R, Sirisanthana T, Supparatpinyo K (2011) Incidence and risk factors of antiretroviral treatment failure in treatment-naïve HIV-infected patients at Chiang Mai University Hospital, Thailand. AIDS Res Ther 8: 42.
19. Rajasekaran S, Jeyaseelan L, Vijila S, Gomathi C, Raja K (2007) Predictors of failure of first-line antiretroviral therapy in HIV-infected adults: Indian experience. AIDS 4: S47-53.